ORIGINAL RESEARCH ARTICLE

Drug Saf 2010; 33 (5): 409-416
0114-5916/10/0005-0409/$49.95/0

Improving Adverse Drug Reaction Reporting in Hospitals

Results of the French Pharmacovigilance in Midi-Pyrénées Region (PharmacoMIP) Network 2-Year Pilot Study

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Abstract

Background: Spontaneous reporting of adverse drug reactions (ADRs) is fundamental to drug safety surveillance (pharmacovigilance); however, substantial under-reporting exists and is the main limitation of the system. Several factors could favour under-reporting.

Objective: The aim of this pilot study was to assess the effect of regular visits of a Clinical Research Assistant (CRA) on the improvement of ADR reporting in non-university hospitals.

Methods: We set up an ADR report collecting system that involved regular visits by a CRA to non-university hospitals, which was similar to a system that already existed in university hospitals in Toulouse, France. Two areas in our region were chosen: Haute Garonne and Gers. We compared firstly the reporting rate (number of reports/number of beds) of total ADRs (i.e. *spontaneously* reported ADRs plus *solicited* ADRs collected by the CRA) and secondly, the percentage of serious ADRs reported by non-university hospitals in these two areas, in 2005 (the year prior to CRA visits) and after the start of CRA visits (2006 until the end of December 2008). We also compared the reporting rate of total ADRs in Haute Garonne and Gers non-university hospitals with those reported during the same period with a control group (the Ariège area, which has a similar number of beds to Gers and that was not visited by the CRA). The characteristics of ADRs collected by the CRA were also described.

Results: A total of 687 reports were collected by the CRA: 40% were classified as serious, including two deaths. The number of ADRs and the reporting rate increased significantly between 2005 and 2008 in non-university hospitals of Haute-Garonne and Gers, but not in Ariège. In Gers, the reporting rate was 3% in 2005 and 25% in 2008. In Haute-Garonne, the reporting rate was 11% in 2005 and 40% in 2008. The difference between the number of spontaneous and solicited reports also increased.

Conclusions: This study shows that regular visits by a CRA increases the number of ADRs collected by a Regional Pharmacovigilance Centre. Another interesting consequence was the rise in spontaneous reporting by healthcare professionals following the set-up of this system. Further assessment of this procedure is necessary for the long-term evaluation of its effectiveness.

Background

Adverse drug reactions (ADRs) are an important cause of morbidity and mortality, accounting for up to 6.5% of all hospital admissions.[1,2] In France, as early as the 1970s, various incidents (both national and European) surrounding medication safety awakened the authorities to the need for a national system of pharmacovigilance, based on a network of 31 Regional Pharmacovigilance Centres (RPVCs) located in clinical pharmacology departments in university hospitals. RPVCs have to collect and evaluate reports of ADRs in their defined geographical area.[3] For example, the Midi-Pyrénées RPVC is located in Toulouse University Hospital (Toulouse is the main city of the Midi-Pyrénées region). In France, prescribers of drugs (physicians, dental surgeons and midwives) or pharmacists are legally required to immediately report 'serious' or 'unexpected' ADRs to their RPVC.[4,5] Other healthcare professionals (nurses, physiotherapists, etc.) can also report ADRs.[3,5] Spontaneous reporting of ADRs is one of the most versatile pharmacovigilance systems because, amongst other advantages, it covers the entire population as well as all drugs throughout their commercial life. Nevertheless, the effectiveness of the system is seriously compromised by under-reporting. Numerous studies have tried to identify factors that influence under-reporting: the main reasons that have been highlighted are non-seriousness of ADRs, uncertainty concerning the causal relationship between the ADR and the drug, forgetting to report and lack of time.[6-11] Other work has demonstrated that having a pharmacovigilance centre nearby increases the number of spontaneous reports.[12]

According to our previous data (Bagheri H, et al. unpublished observations), in Toulouse University Hospitals wards (1642 medical beds) regularly visited by members of the Midi-Pyrénées RPVC, the ADR reporting rate (number of reports/number of beds) in 2005 was approximately 30-fold higher than in non-university hospitals in the Midi-Pyrénées region. This variation between university and non-university hospitals could be explained, at least partly, by the lack of time for reporting procedure: in university hospitals, 'spontaneous reports' should strictly be referred to as 'solicited reports' since most of the ADRs are collected following regular visits to each medical ward by students or residents from the Midi-Pyrénées RPVC. For this reason, it seemed justified to set up, at regional level, an ADR collecting system similar to that existing in Toulouse University Hospitals. Therefore, in 2005, we suggested to the Regional Agency for Hospitalisation in the Midi-Pyrénées region that a project be undertaken for the assignment of a Clinical Research Assistant (CRA) to collect ADRs in public and private sector establishments other than university hospitals. This CRA would also encourage practitioners to undertake ADR reporting.

This project was approved in 2006 and has been funded since then.

The aim of this pilot study was to assess the effect of regular visits of the CRA on ADR reporting in non-university hospitals during the first 2 years of the project. The project is entitled Pharmacovigilance in Midi-Pyrénées region (PharmacoMIP).

Preliminary History of Intervention

The pharmacovigilance awareness campaign in non-university hospitals of Midi-Pyrénées started in October 2000. We suggested that the directors and presidents of Hospital Medical Commissions in public and private non-university hospitals nominate a 'pharmacovigilance correspondent' in their hospitals: 83% were pharmacists, 13.5% were doctors, and nurses or hospital directors accounted for <3%. The Regional Commission for Coordination of Health Vigilances updates this list every year. In addition, since the year 2000, we have organized an annual 3-day pharmacovigilance seminar at the RPVC for healthcare professionals (medical and paramedical) working in these non-university hospitals. People taking part in this seminar are issued a certificate by Toulouse University.

Methods

Study Design

This longitudinal study was undertaken in two administrative areas in our region – Haute Garonne (1 046 338 inhabitants with 1276 medical beds in non-university hospitals) and Gers (172 335 inhabitants with 337 medical beds). Haute Garonne was chosen because of the large number of non-university hospitals and private clinics (n = 41) and Gers (14 non-university hospitals and private clinics) was also included because of the very low number of pharmacovigilance reports and demographic characteristics (high proportion of elderly people). A control group encompassing non-university hospitals not visited by the CRA in Ariège, an administrative area with similar characteristics to Gers (137 205 inhabitants with 356 medical beds), was also selected.

Implementation of the Study

In February 2006, a letter explaining the project was sent out to directors and presidents of Hospital Medical Commissions, and pharmacovigilance correspondents of all the establishments (the letter was signed by the Regional Agency for Hospitalisation, Regional Commission for Coordination of Health Vigilances and RPVC).

From the end of May to November 2006, appointments were made through the pharmacovigilance correspondent for an on-site visit (by a senior member of the RPVC as well as the CRA), to present the project to healthcare professionals within the establishment and to discuss matters of organization. The CRA has a Bachelor of Science degree, and has undergone specific training in pharmacovigilance for 2 months. The pharmacovigilance system in France (notably the existence of a national pharmacovigilance database where all RPVCs record ADRs) was explained. Moreover, the usefulness of contributions from paramedical professionals (nurses, senior nursing staff) to pharmacovigilance activities, especially for certain types of ADRs (those that are non-serious but that affect the quality of life of patients, for example certain ADRs involving the skin)[13] and the fact that data collection and causality assessment would be carried out by the CRA and the RPVC (meaning the doctor only had to report the suspected adverse effect) was underlined.

The CRA visits began in June 2006. Their frequency was determined by the type and size of the establishment, and was generally once every 1 or 2 months. For each visit, the CRA informed the pharmacovigilance correspondent of their intended visit and collected the filed reports (with patient initials, adverse effect and the suspected drug[s]). The CRA completed the observations by referring to the patient's medical records. A follow-up was carried out if necessary. For all other ADR reports received in the Toulouse RPVC, each case was validated by senior members of staff and registered into the French

pharmacovigilance database after assessment of imputability score according to the official French method.[14] A letter with the imputability score plus bibliographical data (if necessary, mainly for an unexpected ADR) was then sent to the healthcare professional reporting the ADR.

Outcome Measures

We compared firstly the reporting rate of total ADRs (i.e. *spontaneously* reported ADRs plus *solicited* ADRs collected by the CRA) and secondly, the percentage of serious ADRs reported by non-university hospitals in Haute Garonne and Gers, in 2005 (the year prior to CRA visits) and after CRA visits (start of 2006 until the end of 2008; although CRA visits began in June 2006, the whole of 2006 was considered as the year 'after CRA visits' for easier analysis and as very few reports were made prior to the visits). Moreover, we also compared the reporting rate of total ADRs in Haute Garonne and Gers non-university hospitals with those reported during the same period by a control group, including non-university hospitals from Ariège (an area not visited by the CRA with a number of beds similar to Gers, used as a control group).

Secondly, characteristics of ADRs collected by the CRA, including seriousness, patient demographics (sex, age), suspected drug(s) and WHO Adverse Reaction Terminology (WHO-ART), are described.[5] Finally, as RPVCs have a duty to respond to enquiries made about drugs, we also analysed the requests for drug information received from the non-university hospitals.

Statistical Analysis

Comparisons of the reporting rate of total (solicited plus spontaneous) ADRs were performed using the χ^2 test for linear trend. The level of significance was $p < 0.05$.

Results

In our first on-site visit, the project was well received by medical teams. The four main reasons of under-reporting suggested by physicians during our visits (before the regular visits of the CRA) were as follows: (i) they were unaware of the type of ADRs to report (especially the lack of understanding of the necessity of reporting serious and expected ADRs already mentioned in the summary of product characteristics [SPC]); (ii) uncertainty about the causal link between medication and ADR; (iii) lack of time; and (iv) fear of being called upon again after making a report to the RPVC.

Collecting Data on Adverse Drug Reactions (ADRs)

A total of 687 reports were collected by the CRA in the whole of 2006 to the end of 2008. Table I shows the number of reported ADRs from 2005 to 2008 in non-university Hospitals from Haute Garonne and Gers (as well as Ariège area selected as the control group). The number of reported ADRs increased from 2005 to 2008 in Haute-Garonne and Gers, but not in Ariège. The difference between spontaneous and solicited reports increased; for example, in Gers, the number of spontaneous reports was 1 in 2007 and 39 in 2008, indicating an increase in spontaneous reporting induced by CRA visits. This was particularly noticeable in Haute Garonne.

The total ADR reporting rate (solicited plus spontaneous reports) increased significantly in Gers and Haute-Garonne (table II). In fact, in Haute-Garonne in 2008, the reporting rate was similar to that observed in the Toulouse University Hospital (42%). In Ariège, the increase was not statistically significant.

Table I. No. of adverse drug reaction (ADR) reports collected by a Clinical Research Assistant (CRA) [solicited reports] and total ADR reports (i.e. spontaneous reports + solicited reports) in non-university hospitals of Haute-Garonne and Gers before (2005) and since CRA visits (2006–2008)[a]

Reports	2005	2006	2007	2008
Solicited reports in Gers	0	26	44	45
Total reports in Gers	11	45	45	84
Solicited reports in Haute-Garonne	0	156	174	242
Total reports in Haute-Garonne	135	291	231	516
Total spontaneous reports in Ariège[b]	1	0	3	4

a The intervention (CRA visits) began in June 2006.

b Ariège area was not visited by the CRA and was used as a control.

Table II. Total adverse drug reaction reporting rate (number of reports/number of beds) in non-university hospitals from the Haute Garonne, Gers and Ariège areas[a,b]

Reports	2005 (%)	2006 (%)	2007 (%)	2008 (%)	p-Value
Total reports in Gers	3	13	13	25	<0.05
Total reports in Haute-Garonne	11	23	18	40	<0.05
Total spontaneous reports in Ariège (control group)	0.3	0	1	1	NS

a Total reports includes both solicited and spontaneous reports.

b The intervention (Clinical Research Assistant visits) began in June 2006.

NS = not significant.

Characteristics of ADRs Collected by the Clinical Research Assistant

ADRs collected by the CRA were mainly observed in the elderly (mean age 69 ± 17 years), and 63% occurred in women. Forty percent were classified as serious, including two deaths – a subarachnoid haemorrhage during treatment with clopidogrel and sunitinib in a 69-year-old man, and anaphylactic shock with intravenous amoxicillin in a 39-year-old woman who was in labour, leading to death of the infant. Another case of note of reversible posterior leukoencephalopathy syndrome in a patient treated with a bevacizumab/doxorubicin regimen with a favourable outcome was also collected.[15]

In Haute-Garonne non-university hospitals, the percentage of serious ADRs was 27% in 2005, 36% in 2006, 48% in 2007 and 28% in 2008. In Gers, 72% of ADRs were serious in 2005, 26% in 2006, 42% in 2007 and 16% in 2008.

Figure 1 shows the main drugs suspected as being the cause of the ADR: primarily, neuropsychotropics (25%, predominantly antipsychotics [48 cases], antiepileptics and antidepressants [41 cases each]) followed by antithrombotics (16%, comprising injectable anticoagulants [86 cases] and oral anticoagulants [12 cases]) and anti-infectives (15%, mainly β-lactams [54 cases], fluoroquinolones [16 cases] and sulfonamides [13 cases]).

Figure 2 indicates ADRs by WHO-ART, mainly cutaneous (20%), neuropsychic (18%), cardiovascular (14%) and gastrointestinal (10%).

Requests for Information about Drugs

During our visits, we recorded 33 requests for information about drugs for the years 2007 and 2008 in the two administrative areas concerned (vs 11 in 2005, i.e. before CRA visits).

Discussion

This longitudinal study shows an increase in ADR reporting from non-university hospitals after the implementation of the new pharmacovigilance programme. Furthermore, comparisons of the reporting rate of ADRs to other non-university hospitals not visited by the CRA also show the beneficial effect of this new system. Supporting the reporting process by regular visits of a member of the RPVC removes some of the obstacles to ADR notification. Moreover, our data also show that spontaneous reporting was induced in establishments regularly visited by the CRA. According to our data, the increase of serious ADR reports did not follow that of total ADR reports, which could be explained by our encouragement

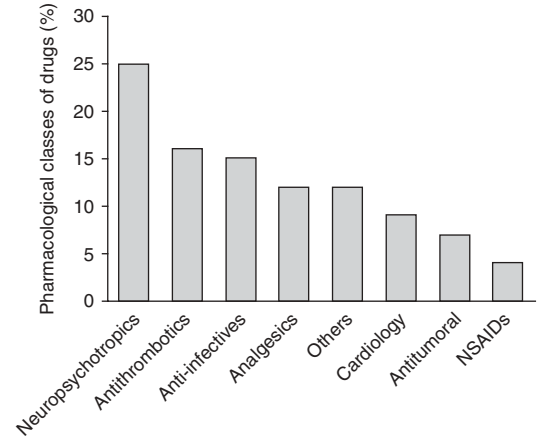

Fig. 1. Pharmacological classes of drugs (%) suspected in adverse drug reaction reports collected by a Clinical Research Assistant.

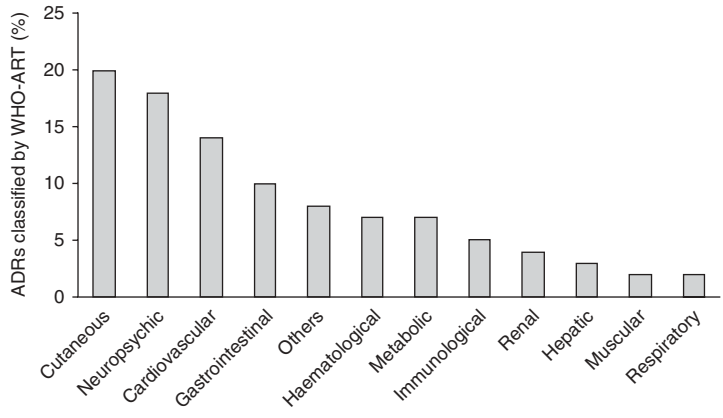

Fig. 2. Adverse drug reactions (ADRs) classified by WHO Adverse Reaction Terminology (WHO-ART [%]) in ADR reports collected by a Clinical Research Assistant.

of healthcare professionals to notify all types of ADRs at the beginning of the project; however, this new programme allowed us to register some previously undetected serious ADRs. Although CRA visits began in June 2006, the whole of 2006 was considered as the year 'after CRA visits' for analysis purposes, because spontaneous reporting in 2006 was rare before the visits began.

As far as we know, this is a relatively new and original method to improve ADR reporting. Several teams have shown that under-reporting could be minimized by different methods, mainly educational visits. Pedros et al.[16] showed that regular interventions of pharmacological staff in different wards of hospitals, based on healthcare management agreements with economic incentives and educational activities, are associated with an improvement in spontaneous reporting. Herdeiro et al.[9,10,17] showed that the implementation of purpose-designed educational programmes for pharmacists and physicians could contribute to improved ADR reporting; however, the effect remained significant only during a limited period. Moreover, two groups indicated that a feedback letter with an assessment of causality, and distribution of a bulletin on drug safety issues could increase the reporting rate.[18,19] Other studies suggested a positive impact of 'economic incentive'.[20,21]

Compared with other methods, our study could be limited by the absence of control groups in the same area (Gers or Haute Garonne); however, the aim of our study was not an interventional trial. A comparison was carried out with a control group (Ariège area), with similar demographic criteria to Gers.

Finally, although the main aim of this project was the evaluation of the improvement of ADR reporting, other aspects of this system should be taken into account. Collecting ADRs leads to dialogue between the clinical pharmacology department (where the RPVC is located) and healthcare professionals. In fact, regular visits encourage healthcare professionals to ask the RPVC for independent information about the use of drugs and the choice for Hospital Drug Committees. This system also facilitates occasional information sessions run by the RPVC within the hospital (e.g. 'latest data in pharmacovigilance' or 'new drugs of the year'). Thus, the RPVC fulfills two tasks at regional level, not only collecting and validating ADRs but also providing information about drug use. These exchanges could be the stepping stone toward a public and independent medical visit. This enables the Clinical Pharmacology Department to access public or private hospitals, whatever their size or type (local or rural etc). Another positive aspect of this system was the raising of awareness among

paramedical professionals (for example nurses) who represent a noteworthy source when collecting ADR reports. Some studies have demonstrated the value of the contribution of nurses to pharmacovigilance activities.[22-24]

Although the cost-effectiveness evaluation of this system was not the aim of the study, we should underline its interest because a CRA costs approximately €35 000 per year (travelling expenses included). Considering the encouraging results after our first assessment, and with the support of the Regional Commission for Coordination of Health Vigilances, we have requested the creation of a second CRA post in order to cover other areas in our region. The consent of the Regional Agency for Hospitalisation for the Midi-Pyrénées area at the end of December 2008 enables us to set up the same system in four other areas (Hautes-Pyrénées [222 368 inhabitants], Tarn and Garonne [206 034], Lot [160 197] and Ariège [137 205]). Considering the large size of the Midi-Pyrénées region, a third CRA agent should allow us to cover the whole region (including the departments of Tarn [377 000 inhabitants] and Aveyron [273 377]). In the long term, it allows us to establish, according to Ramsay's words, a ''bridge rather than a gap'' between clinical pharmacology and health protagonists involved in drug dispensing and use.[25]

Conclusions

This simple and inexpensive system appreciably improves the collection of ADRs in hospitals. Another interesting consequence was the rise in spontaneous reporting by healthcare professionals following the set-up of this system. Further assessment of this procedure is necessary for the long-term evaluation of its effectiveness.

Acknowledgements

The authors would like to thank the Regional Agency of Hospitalisations of Midi-Pyrénées who financially supported the project, as well as the Regional Commission for Coordination of Health Vigilances, who helped to organize the work.

The authors have no conflicts of interest to declare that are directly relevant to the content of this study.

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